UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,366	03/26/2004	J. Yun Tso	GUH-026-101	3678

28120 7590 01/08/2009

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
01/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,366	TSO ET AL.	
	Examiner	Art Unit	
	JAMES L. GRUN	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,40,46,47 and 49-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,40,46,47 and 49-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

0The amendment filed 18 September 2008 is acknowledged and has been entered. Claims 1-38, 41-45, and 48 have been cancelled. Claims 39, 40, 46, 47 and 49-55 remain in the case.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 40, 46, 47, and 52 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with that as claimed. As set forth, absent further written description and guidance from applicant, one would not be assured of the ability to make and use the invention without the requisite structural relationships of complementarity determining regions.

Applicant's arguments filed 18 September 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons of record and as set forth above. As set forth, other than antibodies comprising all of the relevant complementarity determining regions (CDRs) of SEQ ID NOS: 3 and 8 disclosed by applicant (SEQ ID NOS: 5-7 and 10-12) in the proper site on an appropriate antibody heavy or light chain framework, respectively, the skilled artisan cannot envision the detailed structure of the full scope of the encompassed polypeptides as are claimed. Moreover, not knowing, absent further experimentation, which of the recited sequences specifically claimed, or modifications thereof, function and which do not, when, as set forth, even a single change of an amino acid can unpredictably affect structure and antigen-binding function, leads to one having no predictability or expectation of success for the function of any given antibody or antibody modification not including all of the disclosed sequences as CDR sequences in the proper site on an appropriate antibody heavy or light chain framework.

The specification is objected to under 35 U.S.C. § 112, first paragraph, for the reasons of record as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. With regard to claim 40, applicant specifically claims and/or requires the 3B10, 4B2, 10, 17, 24, 25, 26, 27, 31, 41, 50, 60, 87, 3-4A, and 3-11F antibodies.

The specification is objected to under 35 U.S.C. § 112, first paragraph, for the reasons of record as failing to provide an adequate written description of the invention and failing to

provide an enabling disclosure, because the specification does not provide evidence that the biological materials required by the claims are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. With regard to claims 39, 40, 46, 47, 49-51, and 53-55, applicant's disclosure teaches that the AL1 and either of the AL12 or AL13 antibodies are required to determine if one has an antibody reacting to any of the other epitopes of a pleiotrophin protein classed by applicant as "type III" (see e.g. page 18).

Applicant's statement, filed 18 September 2008, that the hybridomas will be deposited in compliance with all the conditions, assurances, and corroborations to satisfy the criteria set forth in 37 CFR §§ 1.801-1.809 within the required time is noted. The rejections of the claims are being held in abeyance as requested by applicant. Applicant is again reminded that information regarding the deposits, such as the name and address of the depository, in addition to the accession numbers of the deposits and the date(s) of the deposits, **must** be added to the specification by means of filing an amendment as required by 37 CFR § 1.809(d).

Claims 39, 40, 46, 47, 49-51, 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant teaches that selected monoclonal antibodies as instantly claimed inhibit selected cellular responses induced by pleiotrophin (PTN), such as tumor cell proliferation or an *in vitro* assay of endothelial cell angiogenesis. However, absent evidence from applicant to the

contrary, it would seem entirely unknown and unpredictable that antibodies capable of neutralizing "signaling transduction activities" were obtainable. The mechanism of action of the exemplified inhibitory antibodies is unknown and it would appear pure speculation on the part of applicant that any of the antibodies inhibit signaling transduction, particularly because it is not clear what applicant intends as encompassed by the activity. Inhibition of receptor binding is listed separately by applicant as an activity, but it is not clear if applicant intends inhibition of receptor binding as inhibitory of a signaling transduction. Random, unguided, and unpredictable experimentation would be required for one to determine if any given antibody were capable of inhibition of signaling transduction, and, lacking any evidence in the specification of such a function, one would not be assured of the predictable ability to obtain and use an antibody with such a function. Such experimentation with no predictability of success is undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39, 40, 46, 47, 49-51, and 53-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 39 and claims dependent thereupon, it is not clear what applicant intends as encompassed by "signaling transduction activities" of pleiotrophin.

Claim 40 is vague in the absence of recitation of deposit accession number(s) to clearly identify the claimed antibody/hybridoma species because, absent the recitation of deposit

accession numbers, it is not clear what structure and properties are encompassed by the named antibodies. In this claim it is not clear what applicant intends as encompassed by "substantially" the same epitope. What degree of binding reduction is sufficient for "substantial" binding competition?

In claim 55, the acronym "PTN protein" should be defined on first presentation.

Applicant's arguments filed 18 September 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

Applicant again urges that the definition of "substantially the same epitope" would guide one to an understanding of the subject matter claimed. This is again not found persuasive for the reasons of record that the degree of binding reduction sufficient for "substantial" binding competition is not clear. Moreover, the encompassed subject matter is not clearly defined because it is well known in the art that antibodies need not bind to the same or overlapping epitope to affect binding of another antibody to a different epitope altered by the binding of the first antibody.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject

matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 39, 40, 46, 49, 50, and 53-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Jäger et al. (Int. J. Cancer 73: 537, 1997), Rauvala (EMBO J. 8: 2933, 1989), Ledoux et al. (J. Histochem. Cytochem. 45: 1239, 1997), Harlow et al., Knight (US 5,675,063), and Czubayko et al. (J. Biol. Chem. 269: 21358, 1994) for reasons of record in the prior rejection of the similar subject matter of these claims.

Claims 39, 40, 46, 49, 50, and 53-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Jäger et al. (Int. J. Cancer 73: 537, 1997), Rauvala (EMBO J. 8: 2933, 1989), Ledoux et al. (J. Histochem. Cytochem. 45: 1239, 1997), Harlow et al., Roes et al. (J. Immunol. Meth. 183:231-237, 1995), Amet et al. (Mol. Cell. Neurosci. 17:1014, 2001), and Czubayko et al. (J. Biol. Chem 269: 21358, 1994) for reasons of record in the prior rejection of the similar subject matter of these claims.

Applicant's arguments filed 18 September 2008 have been fully considered but they are not deemed to be persuasive.

Applicant urges that the references applied in a rejection under 35 U.S.C. § 103 must suggest that one should have made the invention with a reasonable expectation of success rather than suggesting that the invention might be obvious to try. This is not found persuasive in view of the reasons set forth in the rejections of record that one would have been motivated to pursue blocking antibodies specific particularly for the N-terminal region of the protein with a

reasonable expectation of success in view of, among other reasons, the obvious motivations to produce monoclonal antibodies as set forth, the teachings of Czubayko et al. regarding antibodies as a specific drug for blocking the growth factor activity of pleiotrophin, and the cited teachings that the peptide of Rauvala or Jäger et al. elicits antibodies which bind to and block the native protein and that this domain of the protein is exposed for binding as exemplified by the antibodies elicited in Rauvala or Jäger et al. Moreover, as also set forth, blocking antibodies were expected from the teachings of Czubayko et al., and immunization of knock-out mice with various immunogens, in conjunction with notoriously old and well known fusion techniques, would have been reasonably expected to achieve the expected result, i.e. the production of monoclonal antibodies reactive with the immunogenic antigens for which the knock-out mice have been made deficient (Roes et al.). Notwithstanding applicant's assertions to the contrary, one would have reasonably expected that a 14 amino acid peptide has a limited number of epitopes therein, that multiple antibody binding to such a limited region may not be possible or necessary for the function of an oligoclonal antibody specific therefor, and that an antibody specific for a single epitope in such a limited region mimicking the properties of the oligoclonal antibody would have been reasonably obtainable by routine screening. Notwithstanding applicant's assertions to the contrary, intact mice are not the only species usable for monoclonal antibody production and a failure in intact mice does not teach away from, for the reasons of record, the use of rabbits or of knock-out mice. Moreover, and notwithstanding applicant's allegations to the contrary, applicant provides no evidence on the record that anyone other than applicant tried and failed to elicit the inhibitory antibodies as instantly claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR REPLY TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE MAILING DATE OF THIS ACTION. IN THE EVENT A FIRST REPLY IS FILED WITHIN **TWO MONTHS** OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE **THREE-MONTH** SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR REPLY EXPIRE LATER THAN **SIX MONTHS** FROM THE MAILING DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 11 a.m. to 7 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, SPE, can be contacted at (571) 272-0806.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
January 9, 2009

/Ann Y. Lam/
Primary Examiner, Art Unit 1641
January 3, 2009